

EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Berzofsky et al.

Application No. 10/532,374

Filed: April 21, 2005

Confirmation No. 4276

For: METHODS TO PREVENT TUMOR
RECURRENCE BY BLOCKADE OF TGF-
BETA

FILED VIA EFS

Examiner: Sheela J. Huff

Art Unit: 1643

Attorney Reference No. 4239-67016-02

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UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION OF DR. JAY A. BERZOFSKY UNDER 37 C.F.R. § 1.132

I, Jay A. Berzofsky, M.D., Ph.D declare as follows:

1. I am named as co-inventor of U.S. Patent Application No. 10/532,374, filed April 21, 2005. I have read the above-referenced patent application and the Office action dated February 11, 2009.

2. A copy of my *curriculum vitae* is attached hereto as **Exhibit A**. At present, I hold a position as Chief of the Vaccine Branch, Center for Cancer Research, at the National Cancer Institute. I have 34 years of experience in research including work on immunology and biochemistry, vaccines and cancer. I have published over 435 scientific articles in scientific journals and books. I was president of the American Society for Clinical Investigation from 1993-1994, and was Chair of the Medical Sciences Section of the American Association for the Advancement of Science from 2007-2008. By virtue of my education, training, and professional experience, I am knowledgeable about tumor biology.

3. I understand that the Examiner has rejected the claims of the application for allegedly being obvious over Dasch *et al.* (U.S. Patent No. 6,090,383) in view of PCT Patent Application

No. WO 00/01410, Barbera-Guillem (U.S. Patent No. 6,224,866), Rosenblum (U.S. Patent Application No. 2005/0214307), and Zavada *et al.* (U.S. Patent No. 6,297,041) because the combination of references allegedly teach that a compound can “treat tumor recurrence” (Office action at page 4). However, the claimed invention is not directed to *treating* recurrence of a tumor. Instead, the claimed invention is directed to *inhibiting* recurrence of a tumor. The actions of “inhibiting” and “treating” are very different, as methods of inhibiting a tumor recurrence are prophylactic and are used to prevent a tumor from *developing*, whereas methods of treating a tumor recurrence are directed against an *existing* tumor. Moreover, the effectiveness of an agent for *treating* a tumor recurrence does not predict the effectiveness of the same agent for *inhibiting* the recurrence (see paragraphs 5 and 6, below). Thus, it would not be obvious that the same agent would be effective at both inhibiting and treating a tumor recurrence.

4. The Office action alleges that the specification “equates treatment to inhibition/prevention” because “applicant defines treatment as including prophylactic inhibition” (Office action at pages 4 and 5). I disagree with this assessment. The generic word “treatment” is an all-purpose term that refers to many things, including the use of both agents and therapies to inhibit or treat a disease in a subject and, as discussed above, inhibiting and treating are two completely different actions. The specification states that treatment “[r]efers to both prophylactic inhibition of disease (such as tumor recurrence) and therapeutic interventions to alter the natural course of an untreated disease process, such as a tumor growth. Treatment of a tumor includes, for instance, the surgical removal of the tumor. Treatment of a tumor can also include chemotherapy, immunotherapy, or radiation therapy. Two or more methods of treating a tumor can be provided to a subject in combination. Treatment of a subject includes inhibiting or measurably reducing the recurrence of a tumor” (specification at page 17, lines 11-14). As treatment encompasses both inhibition and intervention, treatment cannot be equated exclusively with inhibition.

5. Inhibiting (or preventing) the recurrence of a tumor is very different from treating a tumor after it recurs. Thus, a distinction must be made between *treatment* and *inhibition* of a tumor recurrence. Agents that effectively cause regression of (treat) a recurrent tumor will not necessarily be effective at inhibiting (preventing) the recurrence itself. For example, agents used

to treat pediatric sarcomas, such as Ewing's sarcoma or Alveolar Rhabdomyosarcoma, are ineffective at inhibiting the recurrence of the tumors in most patients, even if the chemotherapeutic agents are effective at treating the recurrence itself (see Pizzo and Poplack (eds.), *Management of Common Cancers of Childhood*, page 1006, right column, 2002, 4th Ed, Lippincott Williams & Wilkins, Philadelphia, PA; Rodriguez-Galindo *et al.*, *Cancer*, 94: 561-569, 2002). Thus, not all agents used to treat a recurrence will be effective at inhibiting a recurrence.

6. The following discussion is a representative example of an agent used to treat recurrence that cannot be used to prevent recurrence. Chemotherapy, usually a platinum-based doublet regimen (cisplatin or carboplatin administered with a paclitaxel, docetaxel, or gencitabine) is the standard of care for locally advanced stage and metastatic non-small cell lung cancer (NSCLC; Schiller *et al.*, *N Engl J Med.*, 346:92-98, 2002). In patients with inoperable *recurrent* local-regionally advanced (stage III) NSCLC, platinum doublet chemotherapy combined with radiation can result in 5-year disease-free survivals of 15-20% (Dillman *et al.*, *J Natl Cancer Inst.*, 88:1210-1215, 1996; Belani *et al.*, *J Clin Oncol.*, 23:3760-3767, 2005). However, the same platinum-based doublet therapy was found in large clinical trials *not to be effective in preventing recurrences* when used in early stage IB NSCLC as “adjuvant therapy” after surgery (Wakelee *et al.*, *Clin Lung Cancer*, 8:18-21, 2006). Thus, one of skill in the art would conclude from this example that therapies that are beneficial in *treating* recurrent tumors are *not necessarily effective in inhibiting recurrence* after treating the disease with primary therapy like surgery.

7. WO 00/01410 discloses the use of an anti-TGF-beta antibody to “to detect or quantify the TGF- β ” and that the “[r]esults from these tests can be used to diagnose or predict the occurrence of recurrence of a cancer” (WO 00/01410, page 24, lines 7-9). The Office alleges that simply because WO 00/01410 discloses that antibodies to TGF-beta can “be used in the diagnosis and treatment of proliferating cells and that the diagnosis also includes diagnosing tumor recurrence . . . one of ordinary skill in the art would immediately envisage that the same antibody that can detect tumor recurrence can also be used in treatment of tumor recurrence” (Office action at page 5). I disagree and would not equate “detection” with “inhibition.”

Antibodies are unpredictable and one of skill in the art would not be able to predict that an antibody used for detection also would be effective at inhibition (or treatment) of tumor recurrence, without first having demonstrated that the antibody can function to both detect and inhibit (or even treat) tumor recurrence. For example, antibodies to Prostate Specific Antigen (PSA) can be used to measure PSA levels to monitor tumor progression or detect or predict tumor recurrence, but these anti-PSA antibodies cannot be used to treat, prevent, or inhibit tumor recurrence. Accordingly, it would not be obvious from a reference that refers to using an antibody for detection purposes, that the same antibody also would be effective at inhibiting tumor recurrence.

8. In summary, based on my education, training, and professional experience, I believe that the term "treatment" cannot be equated exclusively with the term "inhibition," nor can "detection" be equated with "inhibition." In addition, I believe that it would not be obvious to one of skill in the art that the same agent can be effective at both treating a tumor recurrence and inhibiting (preventing) a recurrence.

9. All statements made herein and of my own knowledge are true and all statements made on information are believed to be true; and further, these statements were made with the knowledge that willful false statements and like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements made may jeopardize the validity of the application or any patent issuing thereon.

Date

June 5, 2009

Jay A. Berzofsky, M.D., Ph.D.